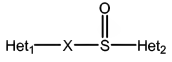
REMARKS

Claims 1-6 and 9-21 are pending, with claims 1, 16 and 17 being independent claims. All the claims are rejected. Applicants respectfully request the Examiner to reconsider and withdraw the outstanding rejection in view of the following remarks.

Claim Rejection under 35 U.S.C. § 103(a)

Claims 1-6 and 9-18 remain rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Brulls, U.S. Patent 6,730,685, in view of Facts & Comparison, in the last Office Action. The rejection has been extended to include new claims 19-21. For the following reasons, the Examiner's rejection is most respectfully traversed by Applicants.

Brulls discloses stable water free liquid formulations for acid labile benzimidazole compounds, such as proton pump inhibitors (PPIs). Brulls discloses formulating the sodium or potassium salts of compounds having the general formula:



All of the examples in Brulls are directed to formulations of the sodium salt of omeprazole, which comprise polyethylene glycol (PEG).

The Office Action alleges that "Brulls teaches pharmaceutical compositions that are combinations of tenatoprazole and H_2-blockers, such as ranitidine. See column 7, lines 22-26."

Applicants respectfully submit that Brulls does not disclose or suggest pharmaceutical compositions that are combinations of specifically tenatoprazole and H_2-blockers, such as ranitidine. The cited portion of Brulls (column 7, lines 22-26) is shown below.

> The formulations may also be used in combination with other drug treatments, such as one or more antibacterial compounds, a motility stimulating drug, an antacid and/or a H_2 -blocker, such as for instance ranitidine.

Applicants submits that the statement in Brulls that "[th]e formulations may also be used in combination with other drug treatments" is meant to encompass that a person may take a dose of the formulation of the proton pump inhibitor and may also take a ***separate dose*** of another drug treatment. Applicants further respectfully submit that the phrase in Brulls that "the formulations may also be used in combination with other drug treatments" is **not** a teaching that the compositions are "combinations of tenatoprazole and H_2-blockers", as alleged in the Office Action. Applicants respectfully submits that one of ordinary skill in the art would not interpret Brulls as disclosing or suggesting combining tenatoprazole and H_2-blockers into a single composition.

The document "Facts and Comparison" relates to ranitidine and provides information on dosing, pharmacokinetics and indications of use. However, this document does not disclose or suggest the combination of tenatoprazole with H2-receptor antagonists.

Applicants respectfully submit that Brulls provides a general description of ***all*** PPIs and does ***not*** specifically name tenatoprazole. In fact, Brulls focuses on omeprazole (See examples). Applicants respectfully notes that the present invention is not directed to a combination of a H2-receptor antagonist with ***any*** PPI, but with tenatoprazole specifically. Applicants respectfully submit that in no way does Brulls disclose or suggest the presently claimed combination of ***specifically*** tenatoprazole with a H2-receptor antagonist.

As described above, the document "Facts and Comparison" merely relates to ranitidine and provides information on dosing, pharmacokinetics and indications of use. Accordingly, as presently cited, Applicants respectfully submits that the document "Facts and Comparison" fails to cure the above-described deficiencies of Brulls. Therefore, even if combined, Brulls and the document "Facts and Comparison" do not disclose or suggest the presently claimed combination of ***specifically*** tenatoprazole with a H2-receptor antagonist.

Moreover, Applicants respectfully submits that the combination of tenatoprazole with H2-receptor antagonists provides results that were not expected based on what was known or expected from other members of the PPI family of compounds. The instant specification states:

> On the contrary, the studies performed by the applicant has shown that the combination of a specific proton pump inhibitor, i.e. tenatoprazole, and a histamine H2-receptor antagonist procures unexpected effects which compared with other proton pump inhibitors and other histamine H2-receptor antagonists, used alone or in combination. More particularly, it has been shown that the combination of tenatoprazole and one or more histamine H2-receptor antagonists enables control of gastric acidity which is markedly superior to that achieved with each of the components used alone, and particularly allows the effective treatment of patients suffering from symptoms and lesions related to gastroesophageal reflux and refractory to standard therapy with a proton pump inhibitor. (See page 3, lines 7-19).

Furthermore, on pages 8 and 9 of the specification, the treatment of patients with symptoms of gastroesophageal reflux is discussed. The treatment was with tentaprazole and ranitidine. The results of the study showed great safety and favorable evolution of the symptom. These results are quite surprising in the light of the prior studies done, for example, with regard to omeprazole as discussed below.

Accordingly, Applicants respectfully submits that the claimed combination of specifically tenatoprazole and a histamine H2-receptor antagonist does provide unexpected results compared to what was known, or would have been expected from other PPIs.

Moreover, Applicants respectfully submits that there is no suggestion or motivation in either Brulls or Facts and Comparisons to combine specifically tenatoprazole and a histamine H2-receptor antagonist into a composition, as required by the present claims. One of ordinary skill in the art, upon reading Brulls, would not be motivated to combine specifically tenatoprazole and a histamine H2-receptor antagonist into a composition for at least two reasons. First, Brulls explicitly discloses that there are significant stability problems with PPIs. Brulls is directed to a method of overcoming the instability of PPIs by forming a specific composition that provides increased stability of PPIs. Second, Brulls also discloses that formulations of a PPI may be used in combination with other drug treatments, not that other active ingredients may be combined in the formulation of Brulls. Therefore, one of ordinary skill in the art would be motivated by the teachings of Brulls not to develop a composition comprising tenatoprazole and a histamine H2-receptor antagonist such as ranitidine.

The Office Action has not provided any suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Applicants respectfully submit that there would not have been a suggestion or motivation in Brulls and the document "Facts and Comparison" or the knowledge generally available to one of ordinary skill in the art, to modify the reference to obtain the Applicants' invention.

Moreover, Applicants respectfully submits that there is no reasonable expectation of success in the combination. The specification of the instant application (page 2, line 26 - page 3, line 6) describes the results of studies reported by PL Peghini et al. (Gastroenterology, 1998) and LB Cross et al. (Ann. Pharmacother., 2002) that investigated various treatment regimes where ranitidine and omeprazole where administered at different times of the day. As indicated in the specification, there did not appear to be an advantage in a combination treatment of omeprazole (a PPI) and ranitidine (a H_2-receptor antagonist). Such teachings would not lead one of ordinary skill in the art to make the combination of a proton pump inhibitor and a H_2-receptor antagonist. In fact, such a teaching would teach-away from such a combination.

Because the claims of the instant application require tenatoprazole, a specific PPI, there is even less likelihood that one would choose this specific PPI to use in combination with an H_2-receptor antagonist, when the prior art teaches against the combination with the most widely used member of the family of PPIs. It is only through the knowledge gained by reading the instant specification that one of ordinary skill in the art would select tenatoprazole from among the various PPIs to combine with a H_2-receptor antagonist, especially when the prior art teaches away from such a combination. Therefore there would not be a reasonable expectation of success in obtaining the Applicants' invention by modifying the cited prior. And, as shown in the study discussed on pages 8-9 of the specification, the combination of tentaprazole and ranitidine works.

We would further have the Examiner consider the prior art and its full teachings, including the two additional documents noted in the Office Action by the Examiner.

The idea of administering both a PPI with a histamine H_2-blocker was first proposed by Peghini *et al.* in 1998 for the particular combination of omeprazole and ranitidine

(mentioned at page 2 of the application). Indeed Peghini *et al.* teaches that administering omeprazole twice a day and ranitidine in the evening to patients suffering from gastro esophageal reflux might be useful. However, it was later demonstrated (in 2002) that such a combined treatment was finally not effective and that, on the contrary, a treatment with omeprazole only was more effective than the combined administration of omeprazole and ranitidine (see Cross *et al.*, mentioned at the end of page 2 of the application).

Therefore, the teaching of Peghini *et al.* is ultimately wrong, but, more importantly, one cannot generalize regarding the combination of any PPI with any histamine H_2-blocker.

The two documents newly noted by the Examiner (Hatlebakk *et al.* and Uchiyama *et al.*) have both been published before the article by Cross *et al.*, i.e. respectively in 1996 and in 1999. Therefore, their teaching has to be nuanced by the later teaching of Cross *et al.*, which makes the point of no advantage in combining omeprazole and ranitidine in the treatment of gastric diseases.

In addition, a full consideration of these two documents actually supports a conclusion of non-obviousness:

Hattelback *et al.* reminds us that the ideal therapy of Gastro-Oesophageal Reflux Diseases (GORD) will have linear pharmacokinetics, a relatively long plasma half-life, duration of action allowing once daily administration, and a stable effect independent of interactions with food, antacids and other drugs. It is stated that the most effective medical therapy for any severity of GORD, particularly in severe oesophagitis, are the PPIs. The substituted benzimidazoles (omeprazole, lansoprazole and pantoprazole) are mentioned.

It is however stated that omeprazole is prone to interaction with the metabolism of other drugs, some of which may be clinically important. Later, this article also states that pharmacokinetic optimization in the treatment of GORD is a question of selecting the suitable substances and administration schemes within each group. Therefore, this article clearly demonstrates that there are no general rules in combining different substances in the treatment of GORD, but on the contrary that extreme care should be taken to avoid any undesirable interactions between active substances. Omeprazole is prone to such interactions.

Therefore, it can not lead one skilled in the art to the present invention, but in fact suggests it would not be obvious to make the proposed combination.

Uchiyama *et al.* (published in 1999) only teaches that the inhibitory effect of tenatoprazole (TU-199) on stimulated gastric acid secretion is more potent than that of omeprazole in dogs. It also teaches that in gastric fistula dogs, the pH-elevation by administration of tenatoprazole is much longer than that of omeprazole and lansoprazole. However this article never envisages the combination of tenatoprazole with another active substance, let alone with a histamine H_2-blocker.

Therefore, there is first no reason to combine the teaching of these two documents, and even when combined together, their teaching cannot lead the one skilled in the art to the claimed invention. On the contrary, it emerges from the teaching of Hattelback that the combination of PPIs with other actives substances can only be done with extreme care because of possible adverse interactions. This teaching has been reinforced later in 2002 by Cross *et al.* since they have shown that a combined treatment was finally not effective and that, on the contrary, a treatment with omeprazole alone was more effective than the combined administration of omeprazole and ranitidine

One can also refer, for example, to the article by WK Fackler *et al.* "Long term effect of H2RA therapy on nocturnal gastric acid breakthrough", Gastroenterology (2002) 122(3) pp. 625-632, the abstract of which is enclosed herewith. This article generally relates to PPIs and histamine H_2-blockers and reaches the conclusion that "there is no difference in acid suppression between PPI twice daily and PPI twice daily + H_2RA after 1 week of combination therapy". This phenomenon is due to H2RA tolerance, that is to say that the efficiency of anti-H2 decreases with time and with the number of intakes in less than one week.

The possible interest in combining a PPI and a histamine H2-blocker comes from the fact that this combination was told to lead to a better control of nocturnal acidity (cf Peghini), but it later appeared that this enhanced efficiency was only observed at the beginning of the treatment (cf more recent articles by Cross and by Fackler). This loss of efficiency is not due to the PPI but to the histamine H_2-blocker. It is therefore surprising that the combination of the same histamine H_2-blocker, with another PPI (tenatoprazole) gives a better result in the

control of gastric acidity as demonstrated in the present application where the results reported in table 2 are results observed after 6 or 8 weeks of treatment.

In addition, when the combination of a PPI and a histamine H_2-blocker was envisaged in the prior art, it was as a treatment combining the intake of one PPI twice daily with the intake of a histamine H_2-blocker only once daily, at bed-time, to better control the nocturnal acidity. On the contrary, the presently claimed invention relates to the combination of tenatoprazole with a histamine H_2-blocker in the same composition, i.e. in the same pharmaceutical vehicle, such a combination leading to satisfactory results after the intake of both active principle only once a day.

In summary, the prior art does not disclose tenatoprazole and a histamine H_2-blocker in the same composition.

The prior art shows that a combination of omeprazole and a H_2-blocker provides no advantage over each separately, and that in fact, a treatment with omeprazole alone is more effective.

The prior art discloses stability problems with PPI's, and suggests that these are overcome by combining them with other drug treatments – not by combining a PPI in a composition with another ingredient.

The prior art discloses there is no general rule in combining different substances in the treatment of gastric hyperacidity.

Therefore, in light of at least the foregoing, Applicants respectfully submits that claims 1-6 and 9-21 are not obvious over Brulls in view of Facts & Comparisons and these claims are allowable. Accordingly, Applicants requests that the rejection of these claims should be withdrawn.

Conclusion

In view of the foregoing remarks, reconsideration of the claims and allowance of the subject application are earnestly solicited. If there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney.

If necessary for a timely response, this paper should be considered as a petition for an Extension of Time, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 13-2725 (#70206.0001USWO).

Respectfully submitted,

17 August 2010

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